

Date of Approval: JAN 12 2006

Handwritten: H-141-007
Div. of Health
Manning

FREEDOM OF INFORMATION SUMMARY

NADA 141-007

DRONTAL Plus TASTE TABS

(praziquantel/pyrantel pamoate/febantel)

Broad Spectrum Chewable Anthelmintic Tablets for Dogs

- 1) For the removal of Tapeworms (*Dipylidium caninum*, *Taenia pisiformis*, *Echinococcus granulosus*, and removal and control of *Echinococcus multilocularis*).
- 2) For the removal of Hookworms (*Ancylostoma caninum*, *Uncinaria stenocephala*), Ascarids (*Toxocara canis*, *Toxascaris leonina*) and Whipworms (*Trichuris vulpis*) in dogs.

Sponsored by:

Bayer HealthCare LLC

Animal Health Division

P.O. Box 390

Shawnee Mission, Kansas 66202

141-007

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FREEDOM OF INFORMATION SUMMARY

1. GENERAL INFORMATION:

- a. **File Number:** NADA 141-007
- b. **Sponsor:** Bayer HealthCare LLC
Animal Health Division
P.O. Box 390
Shawnee Mission, KS 66201
Drug Labeler Code: 000859
- c. **Established Name:** praziquantel/pyrantel pamoate/febantel
- d. **Proprietary Name:** DRONTAL Plus TASTE TABS
- e. **Dosage Form:** Chewable Tablet
- f. **How Supplied:** DRONTAL Plus TASTE TABS are supplied in blister packs by the carton as follows:
Puppies and Small Dogs: 4 strips of 10 tablets (40 tabs/carton)
Medium Sized Dogs: 4 strips of 10 tablets (40 tabs/ carton)
Large Dogs: 3 strips of 10 tablets (30 tabs/carton)
- g. **How Dispensed:** Rx
- h. **Amount of Active Ingredients:** Each tablet for Puppies and Small Dogs contains: 22.7 mg praziquantel, 22.7 mg pyrantel base as pyrantel pamoate, and 113.4 mg febantel.
Each tablet for Medium Dogs contains: 68.0 mg praziquantel, 68.0 mg pyrantel base as pyrantel pamoate, and 340.2 mg febantel.
Each tablet for Large Dogs contains: 136.0 mg praziquantel, 136.0 mg pyrantel base as pyrantel pamoate, and 680.4 mg febantel.

i. **Route of Administration:** Oral

j. **Species/Class:** Canine

k. **Recommended Dosage:** The presence of parasites should be confirmed by laboratory fecal examination. Weigh the animal before treatment. Administer the proper dosage as specified in the following table as a single treatment.

DRONTAL Plus TASTE TABS Dosage Chart

Puppies/Small Dogs* (2 – 25 lbs)		Medium Sized Dogs (26 – 60 lbs)		Large Dogs (45 lbs and greater)	
Body Wt. (lbs)	Taste Tabs	Body Wt. (lbs)	Taste Tabs	Body Wt. (lbs)	Taste Tabs
2 – 4	0.5	26 – 30	1.0	45 – 60	1.0
5 – 7	1.0	31 – 44	1.5	61 – 90	1.5
8 – 12	1.5	45 – 60	2.0	91 – 120	2.0
13 – 18	2.0				
19 – 25	2.5				

*Not for Use in Puppies Less Than 3 Weeks of Age or Dogs Weighing Less Than 2 lbs.

The tablet sizes and dosage table are designed to provide a minimum of 5.0 mg/kg (2.27 mg/lb) each of praziquantel and pyrantel base, and at least 25 mg/kg (11.35 mg/lb) febantel.

The tablets may be offered to the dog by hand. Alternatively, tablets may be given directly by mouth or offered in a small amount of food. Fasting is neither necessary nor recommended prior to or after treatment.

l. **Pharmaceutical Category:** Anthelmintic

m. **Indications:**

DRONTAL Plus (praziquantel/pyrantel pamoate/febantel) TASTE TABS Broad Spectrum Chewable Anthelmintic Tablets are indicated for the removal of Tapeworms (*Dipylidium caninum*, *Taenia pisiformis*, *Echinococcus granulosus*, and removal and control of *Echinococcus multilocularis*) and for removal of Hookworms (*Ancylostoma caninum*, *Uncinaria stenocephala*), Ascarids (*Toxocara canis*, *Toxascaris leonina*) and Whipworms (*Trichuris vulpis*) in dogs.

n. **Effect of Supplement:**

This supplement amends the approved NADA by adding a flavored tablet formulation with the same indications.

2. **EFFECTIVENESS:**

The effectiveness of DRONTAL Plus TASTE TABS is based upon the existing approvals for DRONTAL Plus tablets (NADA 141-007). In addition, four well-controlled laboratory studies were conducted to confirm that the anthelmintic effectiveness of flavored DRONTAL Plus TASTE TABS is equivalent to the original unflavored formulation. One study was designed to evaluate effectiveness of the DRONTAL Plus TASTE TABS against helminths occupying the upper intestinal tract (hookworms). Three studies were conducted according to a common protocol to evaluate the effectiveness of the DRONTAL Plus TASTE TABS against helminths occupying the lower intestinal tract (whipworms). A field study was conducted to confirm palatability.

A. **Evaluation of DRONTAL Plus TASTE TABS Against Hookworm Infection of Dogs, Study No. 151.657.**

The purpose of this well-controlled anthelmintic study was to confirm the effectiveness of DRONTAL Plus TASTE TABS against experimental hookworm (*Ancylostoma caninum* and *Uncinaria stenocephala*) infections of dogs.

Investigator: Robyn Slone, B.S.
Professional Laboratory and Research Service
Corapeake, NC

Animals: Twenty purpose bred beagles (10 male, 10 female), 2 – 2½ months of age.

Dosage Groups:

Group 1: DRONTAL Plus TASTE TABS treated according to the labeled dosage to provide at least 5 mg/kg each of praziquantel and pyrantel base plus at least 25 mg/kg febantel (10 dogs).

Group 2: Untreated (10 dogs)

Route of Administration: Oral

Frequency of Treatment: Once

Duration of Study: 35 days

Study Design: Each dog was experimentally infected with a combination of *A. caninum* and *U. stenocephala* third stage larvae on test day –28. On test day –1 the twenty dogs were randomized into two groups by sex and body weight. On test day 0 group 1 dogs were treated with DRONTAL Plus TASTE TABS according to the label dosage. Group 2 dogs were untreated. On test day 7 the animals were euthanized for recovery of all remaining hookworms.

Parameters Measured: The geometric mean number of each hookworm species/dog recovered at necropsy from both study groups was determined. Percent effectiveness was calculated by comparing the geometric mean number of worms remaining in the DRONTAL Plus TASTE TABS treated group with the geometric mean number of worms retained in the control group.

Results: Adequacy of parasite infections was confirmed in the untreated control dogs. At necropsy adult *A. caninum* and *U. stenocephala* were recovered from all 10 control dogs. (*A. caninum* = 8 - 24 worms/dog, geometric mean = 16.60 worms/dog; *U. stenocephala* = 8 - 16 worms/dog, geometric mean = 13.02 worms/dog). By contrast no *A. caninum* and only one *U. stenocephala* were recovered at necropsy from the 10 dogs treated with DRONTAL Plus TASTE TABS (geometric mean *A. caninum* and *U. stenocephala* counts of 0.0 and 0.07 worms/dog, respectively). Anthelmintic effectiveness of DRONTAL Plus TASTE TABS against *A. caninum* and *U. stenocephala* was 100 and 99.4%, respectively.

Adverse Reactions: One episode of bloody/mucoid stool occurred in a treated puppy on day 1. One episode of watery/profuse stool occurred in a treated puppy on day 3.

Conclusions: A single dose of DRONTAL Plus TASTE TABS administered orally according to the recommended dosage schedule was efficacious against helminths (*i.e.*, *A. caninum* and *U. stenocephala*) residing in the upper intestinal tract of dogs.

B. Evaluation of DRONTAL Plus TASTE TABS Against Natural *Trichuris vulpis* Infections of Dogs, Study Nos. 151.656, 151.682, 151.696.

The effectiveness of DRONTAL Plus TASTE TABS against dogs naturally infected with *Trichuris vulpis* (whipworms) was confirmed with three studies conducted according to a common protocol by two investigators at two study locations. Data from these studies were pooled for final effectiveness confirmation.

Investigators: Dawie Kok, D.Sc (Study 151.656)

Clinvet International (Pty)
Bloemfontein, South Africa

Dwight Bowman, Ph.D. (Studies 151.682, 151.696)

Cheri Hill R&D
Stanwood, MI

Animals: 60 dogs with natural *T. vulpis* infections.

Dosage Groups:

Group 1: DRONTAL Plus TASTE TABS treated according to the labeled dosage to provide at least 5 mg/kg each of praziquantel and pyrantel base plus at least 25 mg/kg febantel (30 dogs).

Group 2: Untreated (30 dogs)

Route of Administration: Oral

Duration of Study: 35 days

Study Design: Each dog was naturally infected with *T. vulpis* as confirmed by pretreatment fecal examination. On test day -1 the dogs were randomized into two treatment groups by sex and body weight. On test day 0, group 1 dogs were treated with DRONTAL Plus TASTE TABS according to the labeled dosage. Group 2 dogs were untreated. On test day 7 the animals were euthanized for recovery of all remaining *T. vulpis*.

Parameters Measured: The geometric mean number of *T. vulpis*/dog recovered at necropsy from both study groups was determined. Percent effectiveness was calculated by comparing the geometric mean number of worms remaining in the DRONTAL Plus TASTE TABS treated group with the geometric mean number of worms remaining in the control group.

Results: Adequacy of parasite infections was confirmed in the untreated control dogs. At necropsy, adult *T. vulpis* were recovered from all 30 control dogs (5-560 *T. vulpis* /dog). Table 1 below lists the geometric means for the treated and control groups in each of the three studies. Data from these studies were pooled for final effectiveness confirmation. Anthelmintic effectiveness of DRONTAL Plus TASTE TABS for removal of *T. vulpis*, as calculated with compiled data from the three studies, was 90%.

Table 1: Geometric Means and Effectiveness Percentages from Three Whipworm Effectiveness Studies			
Study Number	Geometric Mean of Treated Group	Geometric Mean of Untreated Control Group	% Effectiveness
151.656	8.65	60.64	85.74
151.682	3.95	46.87	91.57
151.696	3.93	46.25	91.50

Adverse Reactions: One dog treated with DRONTAL Plus TASTE TABS vomited its tablet dosage within minutes of treatment and was redosed. One dog treated with DRONTAL Plus TASTE TABS vomited within 18 hours of treatment. No other unusual observations or adverse events were observed in any of the dogs during the study.

Conclusions: A single dose of DRONTAL Plus TASTE TABS administered orally according to the recommended dosage schedule, was efficacious against intestinal helminths (i.e. *T. vulpis*) residing in the lower intestinal tract of dogs.

C. Clinical Evaluation of the Palatability of DRONTAL Plus TASTE TABS for Dogs, Study No. 151.551.

The purpose of this field study was to confirm that palatability of DRONTAL Plus TASTE TABS in privately owned dogs.

Investigators: Laird Laurence, D.V.M.
Fredericksburg, TX

Richard Mauldin, D.V.M.
Oklahoma City, OK

Roger Sifferman, D.V.M.
Springfield, MO

Animals: One hundred and fifty-one (151) client owned dogs between 6 months and 14 years of age, weighing between 3.8 pounds and 190 pounds. There were 86 females (61 spayed) and 65 males (42 neutered) representing 34 different breeds. Endoparasite infection was not required for enrollment.

Dosage Group: DRONTAL Plus TASTE TABS were offered to all of dogs according to the labeled dosage, which provides at least 5 mg/kg each of praziquantel and pyrantel base, plus at least 25 mg/kg febantel.

Route of Administration: Oral

Frequency of Treatment: Once

Duration of Study: One day for each dog

Study Design: DRONTAL Plus TASTE TABS were dispensed to owners based on the body weight of their dog(s). Approximately half of the dogs were dispensed whole tablets, and half were dispensed either partial tablets or a combination of whole and partial tablets for testing purposes. DRONTAL Plus TASTE TABS were offered to the pet by the owner at home. Tablets were offered by hand for up to two minutes, and if not consumed in this manner were then placed in a food bowl for an additional two minutes.

Parameters Measured: The dog owner scored the acceptance of the DRONTAL Plus TASTE TABS as follows:

- 1) All Tablets Consumed
- 2) No Tablets Consumed
- 3) Part of Tablets Consumed

Results: Acceptance of DRONTAL Plus TASTE TABS was scored as a success if the dog voluntarily ingested and consumed all of the DRONTAL Plus TASTE TABS within the four minutes the tablets were offered (an owner score of 1). Acceptance was scored as a failure if the tablet(s) were only partially consumed, or if no tablets were consumed within four minutes (an owner score of 2 or 3). Owners reported acceptance scores for 149 of the 151 dogs enrolled. Of these 149 dogs, a total of 133 dogs accepted DRONTAL Plus TASTE TABS (an owner score of 1), for a palatability success rate of 89.3%.

Adverse Reactions: One dog vomited 30 minutes after treatment, and another dog vomited 3 hours following treatment.

Conclusion: DRONTAL Plus TASTE TABS are palatable to dogs of various breeds, weights, and age.

3. **TARGET ANIMAL SAFETY:**

The approval of DRONTAL Plus TASTE TABS required no new target animal safety data as the formulation contains the same amount of active ingredients as the currently approved unflavored DRONTAL Plus Tablets. The approval of the TASTE TABS formulation is based on the effectiveness studies, chemistry, manufacturing and control information, and stability data.

4. **HUMAN SAFETY:**

This drug is intended for use in dogs, which are non-food animals. Because this animal drug is not intended for use in food-producing animals, data on human safety pertaining to drug residues in food were not required for approval of this NADA supplement. Human warnings are provided on the product label as follows: "Keep out of reach of children."

5. **AGENCY CONCLUSIONS:**

The data submitted in support of this NADA satisfy the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act and 21 CFR Part 514 of the implementing regulations. The data demonstrate that DRONTAL Plus TASTE TABS when used under the labeled conditions of use are safe and effective for the removal of tapeworms (*Dipylidium caninum*, *Taenia pisiformis*, *Echinococcus granulosus*, and removal and control of *Echinococcus multilocularis*), and for removal of Hookworms (*Ancylostoma caninum*, *Uncinaria stenocephala*), Ascarids (*Toxocara canis*, *Toxascaris leonina*), and Whipworms (*Trichuris vulpis*) in dogs.

The drug is restricted to use by or on the order of a licensed veterinarian because professional expertise is needed to manage the serious public health concerns associated with the diagnosis and treatment of *Echinococcus granulosus* and *multilocularis*.

Under section 512(c)(2)(F)(iii) of the Federal Food, Drug, and Cosmetic Act, this approval qualifies for THREE years of marketing exclusivity beginning on the date of approval. The three years of marketing exclusivity applies only to the new palatable formulation for which this supplement is approved. The four laboratory studies conducted by the sponsor to demonstrate substantial evidence of effectiveness for the new palatable formulation provided the basis for exclusivity.

According to the Center's supplemental approval policy (21 CFR 514.106), this is a Category II change. The approval of this change is not expected to have any adverse effect on the safety or effectiveness of this new animal drug. Accordingly, this approval did not require a reevaluation of the safety and effectiveness data in the parent application.

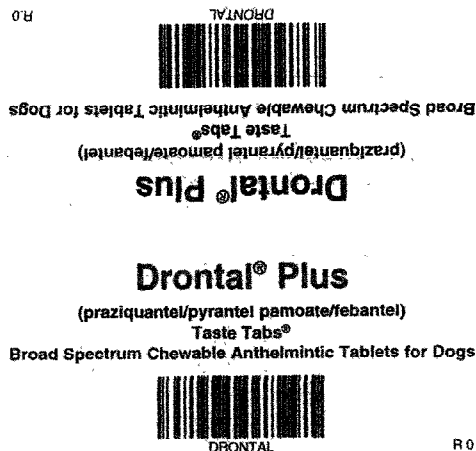
A U.S. patent for DRONTAL Plus TASTE TABS has been applied for. The application is pending.

6. ATTACHMENTS:

Facsimile labeling is attached as indicated below:

- a) Package insert
- b) Blister labeling
 - 1. Small
 - 2. Medium
 - 3. Large
- c) Dispensing carton
 - 1. Small
 - 2. Medium
 - 3. Large

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CAUTION: Federal (U.S.A.) law restricts this drug to use by or on the order of a licensed veterinarian.

DESCRIPTION: Drontal® Plus Taste Tabs® (praziquantel/pyrantel pamoate/febantel) Broad Spectrum Chewable Anthelmintic Tablets for Dogs are available in three tablet sizes. Each size is scored for convenient oral administration.

Each Drontal Plus Taste Tabs Tablet for Puppies and Small Dogs contains 22.7 mg praziquantel, 22.7 mg pyrantel base as pyrantel pamoate and 113.4 mg febantel.

Each Drontal Plus Taste Tabs Tablet for Medium Sized Dogs contains 68.0 mg praziquantel, 68.0 mg pyrantel base as pyrantel pamoate and 340.2 mg febantel.

Each Drontal Plus Taste Tabs Tablet for Large Dogs contains 136.0 mg praziquantel, 136.0 mg pyrantel base as pyrantel pamoate, and 680.4 mg febantel.

ACTION: Drontal® Plus Taste Tabs® Tablets contain three active ingredients having different modes of action and spectra of activity. Praziquantel is active against cestodes (tapeworms). Praziquantel is absorbed, metabolized in the liver and excreted in the bile. Upon entering the digestive tract from the bile, cestocidal activity is exhibited.¹ Following exposure to praziquantel, the tapeworm loses its ability to resist digestion by the mammalian host. Because of this, whole tapeworms, including the scolices, are very rarely passed after administration of praziquantel. In many instances only disintegrated and partially digested pieces of tapeworms will be seen in the stool. The majority of tapeworms are digested and are not found in the feces.

Pyrantel pamoate is active against hookworms and ascarids. Pyrantel pamoate acts on the cholinergic receptors of the nematode resulting in spastic paralysis. Peristaltic action of the intestinal tract then eliminates the parasite.²

Febantel is active against nematode parasites including whipworms. Febantel is rapidly absorbed and metabolized in the animal. Available information suggests that the parasite's energy metabolism is blocked, leading to energy exchange breakdown and inhibited glucose uptake.

Laboratory efficacy and clinical studies conducted with Drontal Plus Anthelmintic Tablets demonstrate that each of the three active ingredients act independently without interference. The combined tablet formulation provides a wide spectrum of activity against the indicated species of intestinal helminths.

INDICATIONS: Drontal® Plus (praziquantel/pyrantel pamoate/febantel) Taste Tabs® Broad Spectrum Chewable Anthelmintic Tablets are indicated for removal of Tapeworms (*Dipylidium caninum*, *Taenia pisiformis*, *Echinococcus granulosus*, and removal and control of *Echinococcus multilocularis*) and for removal of Hookworms (*Ancylostoma caninum*, *Uncinaria stenocephala*), Ascarids (*Toxocara canis*, *Toxascaris leonina*), and Whipworms (*Trichuris vulpis*) in dogs.

CONTRAINDICATIONS: DO NOT USE IN PREGNANT ANIMALS. Dogs treated with elevated levels (6 consecutive days with 3 times the labeled dosage rate) of the combination of febantel and praziquantel in early pregnancy demonstrated an increased incidence of abortion and fetal abnormalities.³ The effects of Drontal® Plus Anthelmintic Tablets on pregnant animals have not been determined.

There are no known contraindications against the use of praziquantel or pyrantel pamoate in dogs.

PRECAUTIONS: Strict hygienic precautions should be taken when handling dogs or feces suspected of harboring *E. multilocularis*. Infected dogs treated for the first time with Drontal® Plus Taste Tabs® Tablets and dogs treated at intervals greater than 28 days may shed eggs in the feces after treatment. The animal should be held in the clinic during this interval and all feces should be incinerated or autoclaved. If these procedures are not possible, the eggs can be destroyed by soaking the feces in a sodium hypochlorite (bleach) solution of 3.75% or greater.⁷ All areas where the animal was maintained or in contact with should be thoroughly cleaned with sodium hypochlorite and allowed to dry completely before reuse.

WARNING: KEEP OUT OF REACH OF CHILDREN.

USE DIRECTIONS

DOSAGE: The presence of parasites should be confirmed by laboratory fecal examination. Weigh the animal before treatment. Administer the proper dosage as specified in the following table as a single oral treatment.

DRONTAL® PLUS TASTE TABS® TABLETS DOSAGE CHARTS

for Puppies and Small Dogs* (2 - 25 lbs.)		for Medium Sized Dogs (26 - 60 lbs.)		for Large Dogs (45 lbs. and greater)	
Body Wt. (lbs.)	No. of Tablets	Body Wt. (lbs.)	No. of Tablets	Body Wt. (lbs.)	No. of Tablets
2 - 4	0.5	26 - 30	1.0	45 - 60	1.0
5 - 7	1.0	31 - 44	1.5	61 - 90	1.5
8 - 12	1.5	45 - 60	2.0	91 - 120	2.0
13 - 18	2.0				
19 - 25	2.5				

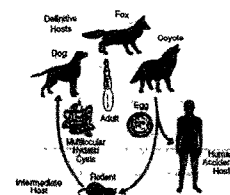
*NOT FOR USE IN PUPPIES LESS THAN 3 WEEKS OF AGE OR DOGS WEIGHING LESS THAN 2 LBS.

ADMINISTRATION: Most dogs find Drontal® Plus Taste Tabs® Tablets very palatable. The tablets may be offered to the dog by hand. Alternatively tablets may be given directly by mouth or offered in a small amount of food. Fasting is neither necessary nor recommended prior to or after treatment.

RETREATMENT: For those animals living where reinfections are likely to occur, clients should be instructed in the steps to optimize prevention; otherwise, retreatment may be necessary. This is true in cases of *Dipylidium caninum* where reinfection is almost certain to occur if fleas are not removed from the animal and its environment. In addition, for control of *Echinococcus multilocularis*, a program of regular treatment every 21 to 26 days may be indicated (see *E. multilocularis* section below).

ECHINOCOCCUS MULTILOCULARIS: *Echinococcus multilocularis* is a tapeworm species usually found in wild canids, including foxes, coyotes and wolves. The parasite has also been identified in domestic dogs and cats and is potentially a serious public health concern because it may infect humans.

The life cycle of the parasite is based on a predator-prey relationship as depicted.



The adult tapeworm is small (1-4mm) and resides in the intestinal tract of the definitive host (wild or domestic canids). Eggs from the adult tapeworm are shed in the feces. Rodents such as mice and voles serve as the intermediate host. Eggs ingested by rodents develop in the liver, lungs and other organs to form multilocular cysts. The life cycle is completed after a canid consumes a rodent infected with cysts. Larvae within the cyst develop into adult tapeworms in the intestinal tract of the canid. Eggs may be passed in the feces of the canid approximately 28 days later.

This parasite poses a serious public health problem because of the possibility for human involvement in the life cycle. If eggs shed by an infected canid are accidentally ingested, a highly pathogenic condition (Alveolar Hydatid Disease) results from development of the cyst stage in humans.

The original geographic distribution of *E. multilocularis* was primarily confined to northern areas of North America. Current evidence indicates migration of the parasite well into the continental United States.^{3,4}

Domestic dogs living in *E. multilocularis* endemic areas that roam freely with the opportunity to catch wild rodents are at risk of infection. Pet owners should be advised on how to minimize this risk. Proper restraint of dogs should be encouraged, along with regular treatment with Drontal® Plus Taste Tabs® Tablets, following the dosing schedule aforementioned and precautions indicated below.

Additional information on the life cycle and epidemiology of this parasite is available in veterinary parasitology texts.^{5,6}

DIAGNOSIS: Diagnosis of *E. multilocularis* in canids is difficult. The adult tapeworm produces no clinical signs of infection. Tapeworm segments (proglottids) are usually not observed in the feces. *E. multilocularis* eggs, observed using microscopic fecal examination procedures, are similar in appearance to those of common species such as *Taenia pisiformis*.

Assistance in the diagnosis of *E. multilocularis* may be available from a state veterinary diagnostic laboratory. Additional information regarding areas where *E. multilocularis* is suspected or has been confirmed may be obtained from area veterinary schools or the Centers for Disease Control in Atlanta, GA.

TREATMENT: Dogs infected with *E. multilocularis* should be treated to prevent exposure of humans to infective eggs and to break the parasite's life cycle.

The dosage of Drontal® Plus Taste Tabs® Tablets for removal of *E. multilocularis* is the same as that indicated for the removal of the other tapeworm species listed on the label. Laboratory efficacy studies conducted with Drontal Plus tablets have demonstrated the recommended dosage is 100% effective.

Under condition of continual exposure to wild rodents, retreatment of the dog at 21-26 day intervals is recommended to prevent the shedding of infectious eggs.

EFFICACY: A total of 176 dogs and puppies with naturally acquired or experimental parasite infections were included in 4 well-controlled laboratory studies to establish the efficacy of Drontal® Plus Anthelmintic Tablets. In addition, 103 dogs and puppies were included in clinical field studies conducted in 5 veterinary clinics at different geographic locations throughout the United States to further evaluate safety and efficacy. These studies included dogs of various sizes, ages and breeds. Data from these studies demonstrated Drontal Plus Anthelmintic Tablets are safe and efficacious for the removal of the parasite species indicated on the label when used as directed.

Results obtained in the laboratory and clinical studies indicate small numbers of hookworm or roundworm eggs may be passed in the feces for up to 7 days after treatment although the worms themselves were eliminated. A follow-up fecal examination should be conducted 2 to 4 weeks after treatment to determine the need for retreatment.

Palatability: Palatability studies with Drontal® Plus Taste Tabs® Tablets were conducted at 3 different veterinary clinics in the United States. These studies included a total of 151 dogs (65 males / 86 females) representing 34 different breeds with body weights ranging from 3.8 – 190 lbs. The tablets were offered free-choice to the dogs by their owners and over 89% of the dogs willingly consumed the tablets.

ADVERSE REACTIONS: None of the 103 dogs treated with Drontal® Plus Anthelmintic Tablets in the clinical field studies exhibited drug-related side effects. Of the 40 dogs treated with Drontal Plus Taste Tabs® Tablets in laboratory studies, two dogs exhibited vomiting, one puppy exhibited bloody/mucoid stool and one puppy exhibited watery/profuse stool.

For customer service or to obtain product information, including Material Safety Data Sheet, call 1-800-633-3796. For medical emergencies or to report adverse reactions, call 1-800-422-9874.

ANIMAL SAFETY: Controlled safety evaluations have been conducted in dogs with Drontal® Plus (praziquantel/pyrantel pamoate/febantel) Anthelmintic Tablets. Dogs receiving up to 5 times the label dosage (35 mg praziquantel, 35 mg pyrantel pamoate and 179 mg febantel per kg of body weight) for 3 consecutive days (3 times the label duration) showed clinical signs of vomiting and non-formed stools. One dog receiving a 3 times labeled dose had elevated SGPT, SGOT, CPK and GGT readings (outside of normal range) at 6 days post-treatment. No additional findings were noted in hematology/clinical chemistry parameters nor were there any treatment-related histological

lesions. Vomiting was the only side effect observed when dogs received a single treatment of 61 mg praziquantel, 61 mg pyrantel pamoate and 305 mg febantel/kg with one dog having an elevated SGPT reading (outside of normal range) at 24 hours post-treatment which had returned to normal by 7 days.

STORAGE CONDITIONS: Drontal® Plus Taste Tabs® Tablets should be stored at or below 77 °F (25 °C).

Un-blistered whole or partial tablets should be stored in a tightly sealed container.

HOW SUPPLIED: Drontal® Plus Taste Tabs® Tablets are available in three tablet sizes:

Code 08758428: 40 tabs/box for Puppies and Small Dogs

Code 08892051: 40 tabs/box for Medium Sized Dogs

Code 08892078: 30 tabs/box for Large Dogs

REFERENCES:

1 Andrews P. 1976 Pharmacokinetic Studies with DRONCIT® in Animals Using a Biological Assay Veterinary Medical Review. 2:154-165.

2 Campbell WC. 1986. The Chemotherapy of Parasitic Infections. J. Parasit. 72(1):45-61.

3 Hildreth MB Johnson MD and Kazacos KR. 1981 A Zoonosis of Increasing Concern in the United States. Compendium for Cont Ed 13(5): 727-740

4 Lieby PD Carney WP and Woods CE. 1970 Studies on Sylvatic Echinococcosis, III Host Occurrence and Geographic Distribution of *Echinococcus multilocularis* in the North Central United States. J. Parasit. 56(6): 1141-1150

5 Georgi JR and Georgi ME. 1990. Parasitology for Veterinarians. W.B. Saunders Co. 118-138
6 Soulsby E.J.L. 1982. Helminths, Arthropods and Protozoa of Domesticated Animals. 7th Edition Lea & Febiger 118-138

7 Craig PS and McPherson CNL. 1988 Sodium Hypochlorite as an Ovicide for Echinococcus. Ann Trop Med. and Parasit. 82(2): 211-213

8 Freedom of Information Summary (FOI) NADA 133-953 Vercom Paste (febantel and praziquantel).

June, 2005

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Bayer

Bayer HealthCare LLC
Animal Health Division
Shawnee Mission, Kansas 66201 USA
NADA 141-007, Approved by FDA

<p>Drontal Plus Taste Tabs Pups & Small Dogs (praziquantel,22.7mg/ pyrantel pamoate,22.7mg/febantel,113.4mg) Bayer HealthCare LLC, Animal Health Div. Lot Exp</p>	<p>Drontal Plus Taste Tabs Pups & Small Dogs (praziquantel,22.7mg/ pyrantel pamoate,22.7mg/febantel,113.4mg) Bayer HealthCare LLC, Animal Health Div. Lot Exp</p>
<p>Drontal Plus Taste Tabs Pups & Small Dogs (praziquantel,22.7mg/ pyrantel pamoate,22.7mg/febantel,113.4mg) Bayer HealthCare LLC, Animal Health Div. Lot Exp</p>	<p>Drontal Plus Taste Tabs Pups & Small Dogs (praziquantel,22.7mg/ pyrantel pamoate,22.7mg/febantel,113.4mg) Bayer HealthCare LLC, Animal Health Div. Lot Exp</p>
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REVISION HISTORY

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<p>Drontal Plus Taste Tabs Medium Sized Dogs (praziquantel,68mg/ pyrantel pamoate,68mg/febantel,340.2mg) Bayer HealthCare LLC, Animal Health Div. Lot Exp</p>	<p>Drontal Plus Taste Tabs Medium Sized Dogs (praziquantel,68mg/ pyrantel pamoate,68mg/febantel,340.2mg) Bayer HealthCare LLC, Animal Health Div. Lot Exp</p>
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Taste Tabs[®]
Drontal Plus

(praziquantel/pyrantel pamoate/febantel)

Broad Spectrum Chewable Anthelmintic
For Puppies and Small Dogs (2-25 lbs.)



For Puppies &
Small Dogs
(2-25 lbs.)

For Puppies & Small Dogs
(2-25 lbs.)

40 Taste Tabs (4 strips of 10 Tablets)

40 Taste Tabs[®] (4 strips of 10 Tablets)

Taste Tabs[®]
Drontal Plus

(praziquantel/pyrantel pamoate/febantel)

Broad Spectrum Chewable Anthelmintic
For Puppies and Small Dogs (2-25 lbs.)

CAUTION: Federal (U.S.A.) law restricts this drug to
use by or on the order of a licensed veterinarian



Bayer HealthCare LLC, Animal Health Division
Shawnee Mission, Kansas 66201 USA
NADA 141-007, Approved by FDA

WARNING: KEEP OUT OF REACH OF CHILDREN

Drontal Plus
(praziquantel/pyrantel pamoate/febantel)



Broad Spectrum
Chewable Anthelmintic
CAUTION: Federal (U.S.A.)
law restricts this drug to
use by or on the order of
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Bayer HealthCare LLC, Animal Health Division
Shawnee Mission, Kansas 66201 USA
NADA 141-007, Approved by FDA

40 Taste Tabs[®] (4 strips of 10 Tablets)

Taste Tabs[®]
Drontal Plus

(praziquantel/pyrantel pamoate/febantel)

Broad Spectrum Chewable Anthelmintic
For Puppies and Small Dogs (2-25 lbs.)

CAUTION: Federal (U.S.A.) law restricts this drug to
use by or on the order of a licensed veterinarian



Bayer HealthCare LLC, Animal Health Division
Shawnee Mission, Kansas 66201 USA
NADA 141-007, Approved by FDA

WARNING: KEEP OUT OF REACH OF CHILDREN

Lot No.
Exp. Date
06730428, R.O.

Small Dog Thermoform

Each Drontal Plus Taste Tab[®] Tablet contains: 22.7 mg praziquantel, 22.7 mg pyrantel base as pyrantel pamoate, and 113.4 mg febantel.

Indications: For removal of tapeworms (*Oxyuris canis*, *Taenia platyura*, *Echinococcus granulosus*, and neonatal and control of *Echinococcus multilocularis*) For removal of hookworms (*Ancylostoma caninum*, *Uncinaria stenocephala*, *Acanthocheilichia canis*, *Tomoxys leonae*), and Whipworms (*Trichostrongylus axei*) in dogs.

Dosage: The presence of parasites should be confirmed by laboratory fecal examination. Weigh the animal before treatment. Administer the proper dosage as specified in the following table on a single oral treatment.

Body Wt. (lbs.)	No. Taste Tabs (2-25 lbs.)
2-4	0.5
5-7	1.0
8-12	1.5
13-18	2.0
19-25	2.5

*Not for use in puppies less than 3 weeks of age or dogs weighing less than 2 lbs.

Administration: Most dogs find Drontal Plus Taste Tabs very palatable. The tablets may be offered to the dog by hand. Alternatively, tablets may be given directly by mouth or offered in a small amount of food. Fasting is neither necessary nor recommended prior to or after treatment.

Contraindications: DO NOT USE IN PREGNANT ANIMALS. The effects of Drontal Plus Taste Tabs on pregnant animals have not been determined.

Storage Conditions: Drontal Plus Taste Tabs should be stored at or below 77°F (25°C). Unblistered whole or partial tablets should be stored in a tightly sealed container.

Consult package insert for further details.



Bayer HealthCare LLC, Animal Health Division
Shawnee Mission, Kansas 66201 USA
NADA 141-007, Approved by FDA
For customer service or to obtain product information, including Material Safety Data Sheet, call 1-800-33-3786.
For medical emergencies or to report adverse reactions call 1-800-421-5874.
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Medium Dog Thermoform

Drontal Plus

CAUTION: Federal (U.S.A.) law restricts this drug to use by or on the order of a licensed veterinarian.



For Medium
Sized Dogs
(26-60 lbs.)

For Medium Sized Dogs
(26-60 lbs.)

40 Taste Tabs® (4 strips of 10 Tablets)

Drontal Plus
(praziquantel/pyrantel pamoate/fenbendazole)

Broad Spectrum Chewable Anthelmintic
For Medium Sized Dogs (26-60 lbs.)

CAUTION: Federal (U.S.A.) law restricts this drug to use by or on the order of a licensed veterinarian.



Bayer HealthCare LLC, Animal Health Division
Shawnee Mission, Kansas 66201 USA
NADA 141-007, Approved by FDA

Each Drontal® Plus Taste Tab® Tablet contains
68.0 mg praziquantel, 68.0 mg pyrantel base
as pyrantel pamoate, and 340.2 mg fenbendazole

WARNING: KEEP OUT OF REACH OF CHILDREN

Drontal Plus
(praziquantel/pyrantel pamoate/fenbendazole)

Broad Spectrum
Chewable Anthelmintic
CAUTION: Federal (U.S.A.)
law restricts this drug to
use by or on the order of
a licensed veterinarian.



Bayer is the Bayer Cross, Drontal and Taste Tabs
are registered trademarks of Bayer

40 Taste Tabs® (4 strips of 10 Tablets)

Drontal Plus
(praziquantel/pyrantel pamoate/fenbendazole)

Broad Spectrum Chewable Anthelmintic
For Medium Sized Dogs (26-60 lbs.)

CAUTION: Federal (U.S.A.) law restricts this drug to use by or on the order of a licensed veterinarian.



Bayer HealthCare LLC, Animal Health Division
Shawnee Mission, Kansas 66201 USA
NADA 141-007, Approved by FDA

Lot No.
Exp. Date
05/02/05 R3

WARNING: KEEP OUT OF REACH OF CHILDREN

Each Drontal® Plus Taste Tab® Tablet contains: 68.0 mg praziquantel, 68.0 mg pyrantel base as pyrantel pamoate, and 340.2 mg fenbendazole.

Indications: For removal of Tapeworms (*Dipylidium caninum*, *Taenia platyura*, *Echinococcus granulosus*, and removal and control of *Echinococcus multilocularis*). For removal of hookworms (*Uncinostoma caninum*, *Uncinostoma stenocephalum*), Ascarids (*Toxocara canis*, *Toxascaris leonina*), and Whipworms (*Trichuris vulpis*) in dogs.

Dosage: The presence of parasites should be confirmed by laboratory fecal examination. Weigh the animal before treatment. Administer the proper dosage as specified in the following table as a single oral treatment.

Drontal Plus Taste Tabs Tablets for Medium Sized Dogs (26-60 lbs.):

Body Wt. (lbs.)	No. Taste Tabs
26-30	1.0
31-44	1.5
45-60	2.0

Administration: Most dogs find Drontal Plus Taste Tabs Tablets very palatable. The tablets may be offered to the dog by hand. Alternatively, tablets may be given directly by mouth or offered in a small amount of food. Feeding is neither necessary nor recommended prior to or after treatment.

Contraindications: DO NOT USE IN PREGNANT ANIMALS. The effects of Drontal Plus Taste Tabs Tablets on pregnant animals have not been determined.

Storage Conditions: Drontal Plus Taste Tabs Tablets should be stored at or below 77° F (25° C). Unblistered whole or partial tablets should be stored in a tightly sealed container.

Consult package insert for further details.



Bayer HealthCare LLC, Animal Health Division
Shawnee Mission, Kansas 66201 USA
NADA 141-007, Approved by FDA

For customer service or to obtain product information, including Material Safety Data Sheet, call 1-800-933-3739.

For medical emergencies or to report adverse reactions call 1-800-452-9874.

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Large Dog Thermoform

Taste Tabs **Drontal Plus** (praziquantel/pyrantel pamoate/febantel)



30 Taste Tabs® (3 strips of 10 Tablets)

Taste Tabs® **Drontal Plus** (praziquantel/pyrantel pamoate/febantel)

Broad Spectrum Chewable Anthelmintic
For Large Dogs (45 lbs. and greater)

CAUTION: Federal (U.S.A.) law restricts this drug to use by or on the order of a licensed veterinarian.



Bayer HealthCare LLC Animal Health Division
Shawnee Mission, Kansas 66201 USA
NADA 141-007, Approved by FDA

Each Drontal® Plus Taste Tab® Tablet contains
136.0 mg praziquantel, 136.0 mg pyrantel base
as pyrantel pamoate, and 680.4 mg febantel

30 Taste Tabs (3 strips of 10 Tablets)

Drontal Plus (praziquantel/pyrantel pamoate/febantel)

Broad Spectrum
Chewable Anthelmintic
CAUTION: Federal (U.S.A.)
law restricts this drug to
use by or on the order of
a licensed veterinarian.



Bayer, the Bayer Cross, Drontal and Taste Tab
are registered trademarks of Bayer

30 Taste Tabs® (3 strips of 10 Tablets)

Taste Tabs® **Drontal Plus** (praziquantel/pyrantel pamoate/febantel)

Broad Spectrum Chewable Anthelmintic
For Large Dogs (45 lbs. and greater)

CAUTION: Federal (U.S.A.) law restricts this drug to use by or on the order of a licensed veterinarian.



Bayer HealthCare LLC Animal Health Division
Shawnee Mission, Kansas 66201 USA
NADA 141-007, Approved by FDA

Each Drontal® Plus Taste Tab® Tablet contains
136.0 mg praziquantel, 136.0 mg pyrantel base
as pyrantel pamoate, and 680.4 mg febantel

Each Drontal® Plus Taste Tab® Tablet
contains: 136.0 mg praziquantel, 136.0 mg
pyrantel base as pyrantel pamoate, and
680.4 mg febantel.

Indications: For removal of tapeworms
(*Oxyuris caninum*, *Isospora*, *Trichostrongylus axei*,
Echinococcus granulosus, and removal
and control of *Echinococcus multilocularis*).
For removal of hookworms (*Ancylostoma
caninum*, *Uncinaria stenocephala*).
Ascarids (*Toxocara canis*, *Toxascaris
leoniae*), and Whipworms (*Trichuris vulpis*)
in dogs.

Dosage: The presence of parasites
should be confirmed by laboratory fecal
examination. Weigh the animal before
treatment. Administer the proper dosage
as specified in the following table as a
single oral treatment.

Drontal Plus Taste Tab
Tablets for Large Dogs
(45 lbs. and greater)

Body Wt. (lbs.)	No. Taste Tabs
45-60	1.0
61-90	1.5
91-120	2.0

Administration: Most dogs find Drontal
Plus Taste Tab Tablets very palatable.
The tablets may be offered to the dog by
hand. Alternatively, tablets may be given
directly by mouth or offered in a small
amount of food. Feeding is neither
necessary nor recommended prior to or
after treatment.

Contraindications: DO NOT USE IN
PREGNANT ANIMALS. The effects of
Drontal Plus Taste Tab Tablets on
pregnant animals have not been
determined.

Storage Conditions: Drontal Plus Taste
Tab Tablets should be stored at or below
77° F (25° C). Un-dissolved whole or partial
tablets should be stored in a tightly sealed
container.

Consult package insert for
further details



Bayer HealthCare LLC Animal Health Division
Shawnee Mission, Kansas 66201 USA
NADA 141-007, Approved by FDA

For customer service or to obtain product
information, including Material Safety
Data Sheet, call 1-800-633-3796

For medical emergencies or to report
adverse reactions call 1-800-422-9833

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Lot No.
Exp. Date
06/02/06, R2